QM MM calculations of aged AChE inhibited by the Organophosphorus compounds sarin, DFP and mipafox

Iris Mangas (PQ)[1,2,3,*]; Palmer Taylor (PQ)[2]; Zoran Radić (PQ)[2]; Tanos C. C. Franca(PQ)[3,4]

*imangas@ime.eb.br

[1]*Institute of Bioengineering. Unit of Toxicology and Chemical Safety. University "Miguel Hernandez" of Elche. Alicante, Spain.*
[2]*Department of Pharmacology, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA 92093 United States.*
[3]*Laboratório de Modelagem Aplicada a Defesa Química e Biológica, Instituto Militar de Engenharia, Rio de Janeiro, Brazil.*
[4]*Center for Basic and Applied Research, Faculty of Informatics and Management, University of Hradec Kralove, Hradec Kralove, Czech Republic.*

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Introduction

Irreversible inhibition of acetylcholinesterase (AChE) is the primary mechanism of action of many organophosphorus compounds (OPs), including pesticides as mipafox and highly toxic nerve agents as sarin. These compounds exert their acute toxicity through phosphorylation of the active site serine. Inhibited AChE can be reactivated by cleavage of the Ser-P bond either spontaneously or through a reaction with nucleophilic agents such as an oxime. The inhibited AChE adduct can also lose part of the molecule by progressive dealkylation over time in a process called aging. Aged enzyme cannot be reactivated[1,2]. It has been suggested that AChE inhibited by mipafox is not reactivatable but not aging reaction was observed in kinetics and mass spectrometry experiments[3]. Here our goal was to study by QM/MM the aging reaction of hAChE inhibited by the OPs diisopropylfluorophosphate (DFP), sarin and mipafox.

Results and Discussion

The molecular structures of the aged hAChE by mipafox, DFP and sarin were built by homology modeling using, as template, the crystal structure of the aged Tabun-inhibited hAChE. The QM regions were considered to include amino acids Asp74, Tyr86, Gly121, Tyr133, Glu202, Ala204, Trp236, Phe 295, Phe297, Glu334, Tyr337, Tyr341, His447, and the corresponding OP conjugated at Ser203. The distances between atoms separated by dealkylation were fitted in the Spartan software[4] (Figure 1). Plots of activation energy (calculated with Gaussian03®) *versus* the distance of atom separation during dealkylation in the molecular modeling experiments may indicate that for mipafox, eventual aging would require higher activation energy. With sarin and DFP however, for which aging was observed in MS, the activation energy is lower and, consequently, aging is more likely. This is the first observation reported of an AChE inhibited by OPs where no reactivation has been observed in non-aging OP-inhibited AChE (Figure 2).

Conclusions

Computational molecular modeling has shown energetically preferred aging in the cases of OP-AChE conjugates formed by sarin and DFP as opposed to any of those formed by mipafox.

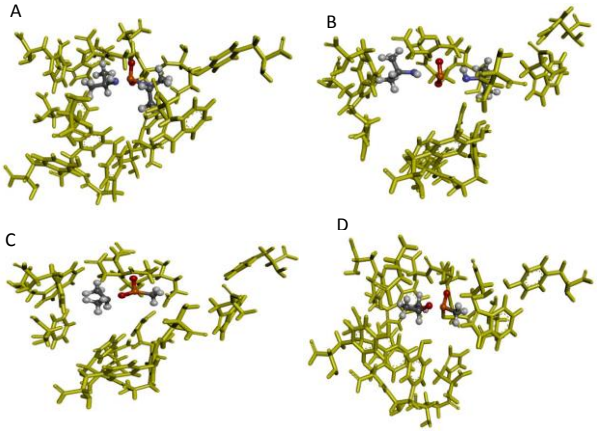

Figure 1. Molecular structures of hAChE aged with mipafox (A, B), DFP (C) and sarin (D).

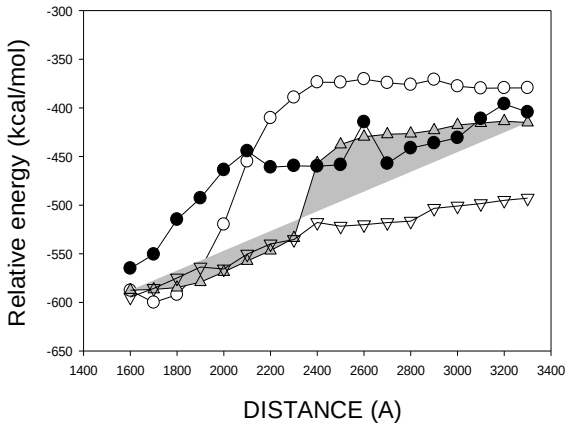

Figure 2. Variation of relative energy with the distance between O(Ser203)-P(OP) for the aging mechanisms. Black circles: sarin aging, white circles: mipafox aging, gray triangles: mipafox at both sites and white triangles: DFP.

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References

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